REMARKS

The above-noted amendments to the claims, including the addition of new claims 20-32, are respectfully submitted in response to the official action dated April 4, 2008. New independent claims 20 and 26 correspond to original claims 1 and 11 with the exception that they are specifically limited to the use of an anti-inflammatory steroid as the first medicament and a bronchodilator as the second medicament. These limitations are not only set forth in the original claims filed in this application but are fully supported in the specification, including at ¶ [0022] and in other portions of the specification. Thus, no new matter is included in these amendments.

Claims 6-9 and 12 have been rejected as being unpatentable under 35 U.S.C. § 112, first paragraph. The Examiner contends that these claims fail to meet the written description requirement, particularly because these claims include not only the first and second particulate medicaments, but also the pharmaceutically acceptable salts, solvates or salt solvates thereof. The Examiner contends that the specification does not disclose specific solvates or salt solvates of these medicaments, and then states that it is generally accepted in the art that the formation of particular solvate or hydrate for a given compound is unpredictable, citing Vippagunta *et al.* therefor. This rejection is respectfully traversed for the reasons set forth hereinafter.

The Examiner does not deny that for every compound or medicament covered by the present claims including the specific anti-inflammatory steroids and bronchodilators set forth herein, there are numerous salts, solvates (including hydrates) and salt solvates which can be produced therefrom. The citation of Vippagunta *et al.*, if anything, supports applicant's position in this regard. This article, published more than a year before

the priority date of the present application, sets forth a detailed analysis for the "prediction and characterization" of polymorphs and solvates. The alleged lack of written description in this case does not relate to the established art of predicting these compounds, but merely to whether one of ordinary skill in the art would know how to produce them from the present disclosure. Indeed, the rejection under the first paragraph of § 112 appears to be in error, the Examiner apparently referring to that portion of the first paragraph of § 112 referring to the manner and process of making and using; namely, the enablement requirement thereof. Certainly the presently claimed invention is fully described in the present specification and claims. In either event, however, even in the Vippagunta *et al.* article, there is no contention, nor could there be, that those of ordinary skill in this art could not produce the various solvates of the drug components thereof. It is the prediction and characterization thereof which is the subject of this article, and indeed more than a year before the filing date of the present application this article provides significant tools even for such prediction and characterization. Again, however, this is not the alleged defect in these claims, and it is therefore respectfully submitted that those of ordinary skill in this art would clearly know how to produce the various salts, solvates or salt solvates of the medicaments hereof, even if they couldn't predict or characterize those solvates. It is further noted that, irrespective of these arguments, new claims 20-32 are all specifically limited to the use of an anti-inflammatory steroid as the first particulate inhalant medicament and a bronchodilator as the second particulate inhalant medicament, thus narrowing the scope of each of these claims as compared to claims 1 and 11 herein. These claims certainly meet all of the requirements of § 112. It

is therefore respectfully requested that this rejection be withdrawn.

Claims 1-3 and 5-19 have been rejected as being unpatentable over Trofast and Keller in view of Ward *et al.* under 35 U.S.C. § 103(a). Keller is said to disclose a dry powder composition in Example 8 which includes 0.2% formoterol fumarate dihydrate, 0.5% glycopyrrolate, 0.5% magnesium stearate, and 98.8% lactose monohydrate. Keller further is quoted as stating that in principle . . . "the constituents can be mixed with one another in any desired sequence. . . ." Keller is also said to disclose use of the dry powder formulation in multidose dry powder inhalers (MDPI), as well as the use of magnesium stearate with certain drugs such as formoterol. This reference is also said to disclose that moisture creates problems in these inhalers.

The Examiner relies on Trofast as also disclosing dry powder formulations for inhalation for use in inhalers such as multidose inhalers, which can be dry powder inhalers. Example 6 of Trofast is said to disclose dry powder compositions of formoterol, lactose and budesonide in which the lactose and formoterol are mixed, micronized and treated according to the method of WO 95/05805, budesonide is added and the mixture is remixed, micronized and agglomerated. Trofast is also said to disclose that when formoterol and budesonide are present in the same formulation, the molar ratios range broadly. Finally, Ward *et al.* is relied upon as teaching methods for oral and pulmonary delivery of pharmaceuticals in which the powder formulation is used in a dry powder inhaler in which the pharmaceutical acts as its own carrier present as micro-fine particles of 1 to 10 microns and larger carrier particles with an AVD of 10 to 2000 microns, most preferably 50 to 100 microns.

The Examiner then recognizes that Trofast lacks explicit teachings of the order of steps, but this is said to be

cured by Keller. Furthermore, Trofast is said to lack teaching of the volume median diameter of the carrier particles of from 50 to 250 microns, but this is said to be cured by Ward *et al.* The references are said to be combinable because they all teach dry powder formulations for inhalation. It is said to be obvious from Keller to adjust the order of mixing, and based on Ward *et al.*'s teachings, it would have been recognized that carrier particles with volume median diameters ranging from 50 to 250 microns would be swallowed upon inhalation. It was further stated that it would have been obvious to reasonably expect success in modifying Trofast's invented formulations to utilize lactose carriers with the claimed VMD range because lactose is said to be a well-known carrier.

As for the order in which the different components are combined, Keller is said to teach that the ingredients can be mixed in any desired sequence. This is said to encompass the blending of a portion of first active particles with carrier particles to obtain a first mixture, combination of a second active with the first mixture to obtain a second mixture, and finally admixture of the remaining first active particles to obtain a dry powder formulation.

Turning to claim 4, the amounts of active in Keller and Trofast are said to be sufficient to form a monolayer, and as for the "consisting of" language of claim 11, Trofast is said to teach compositions containing solely first and second medicaments and a carrier.

Turning to the data in the specification (Tables 1-4) demonstrating the homogeneity of dry powders produced by applicant's method, this is said not to be convincing because it lacks comparison with methods of the prior art. Claims 1-9 are said to be open to a broad range of first and second medicaments and thus, even if the data were indicative of structural modification, the limited scope of the data would be

ineffective. The Examiner then comments upon the broad range of some of the claim limitations.

In response to applicant's arguments, with regard to the prior art not specifically teaching the formation of a monolayer, Keller is said to teach that the ingredients can be mixed in any order. As for applicant's identification of a problem in forming a ternary mixture, there is said to be no data demonstrating the criticality of the order of steps, and it is said to be unclear what the actual problem was that applicant solved. As for Ward *et al.*'s teaching away from the invention, focusing on compositions without a separate carrier, the Examiner merely contends that Ward *et al.* was relied on solely as a secondary reference to demonstrate use of inert carriers with VMD of about 50 to 250 microns. Finally, regarding Trofast's teaching particle sizes of less than 10 microns, this is said to rest on the implication that an ordinarily skilled artisan would not have recognized the latent advantage of using non-respirable carrier particles such as the lowered likelihood of irritation of the pulmonary tissue as a result of contacting with less foreign material, especially where an individual inhaling the composition was lactose intolerant. This rejection is respectfully traversed in view of the above amendments and arguments and for the reasons set forth hereinafter.

Irrespective of all of the detailed arguments presented by the Examiner with respect to each of the three references, their combination, and the elements which they teach, the following is clear beyond doubt:

None of the art teaches the present invention; namely, a specific method and composition which utilizes a sequence in which a carrier is mixed with a first portion of a first particulate inhalant medicament to create a monolayer on a carrier, the first mixture is mixed with a second particulate inhalant medicament to form a second mixture, and the second

mixture is mixed with a second portion of the first particulate inhalant medicament to form the dry powder inhalation compositions hereof. With no teaching of this method, the Examiner relies almost exclusively upon the comment in Keller at column 8, lines 53-59 to the effect that "in principle, the constituents can be mixed with one another in any desired sequence, where, however, mixing should expediently be carried out in such way that the particles of the constituents — apart from the adhesion to the carrier particles — are essentially retained as such, i.e. are not destroyed, for example, by granulation and the like." The overall tenor of the specification, and in fact the discussion immediately succeeding this quotation, makes it clear that this patentee is only discussing the sequence in which each of the ingredients is added, with no reference whatsoever to the use, in any way, of any portion(s) of any of the ingredients. There is no reference whatsoever to applicant's sequence in which a portion of the first medicament is coated on the carrier to form a monolayer, and after the second medicament is applied thereto, a further portion of the first medicament is applied. Essentially, the Examiner has taken the position that this simply cannot be patentable. Applicant clearly disagrees.

The data in the present specification, including that in Example 1, establishes that in a wide range of compositions the homogeneity exhibited was extraordinary. The pharmaceutical performance in terms of uniformity of delivered dose and fine particle dose gave excellent results as shown therein. On the other hand, the prior art itself establishes that the preparation of homogeneous mixtures is not a simple matter, particularly in connection with inhalant medicaments of the present type. Methods of producing ternary mixtures which are homogeneous and are useful with suitable dry powder inhalers in order to provide dose uniformity, reliability and uniform

dispersion of the plurality of medicaments are clearly needed, and applicant has supplied them. This invention is clearly worthy of patenting.

The reasoning as to why a person skilled in the art would have combined *Trofast* with *Ward* and *Keller* to arrive at the presently claimed invention is also not sustainable. As acknowledged by the Examiner, *Trofast* does not teach the order of mixing the medicaments and the carrier as recited in the present claims, nor in fact does it suggest the VMD of the particulate carrier material. Indeed, there is nothing in Trofast which teaches or suggests that the order of mixing of the ingredients is at all significant, nor that it would in any way affect the properties of the dry powder formulations produced thereby.

The Examiner has relied upon Keller to address the claimed recitations with respect to the critical limitation regarding the order of mixing of the ingredients. Keller, however, teaches that an active ingredient, an excipient (*i.e.*, magnesium stearate) and a carrier can be mixed "in any order." As Applicant has already argued, although Keller states that a pharmaceutically inactive carrier, a pharmaceutically active compound and magnesium stearate can be mixed with one another in any desired sequence, there is no teaching of how two active ingredients and an inactive carrier should be combined. Furthermore, there is no suggestion that one of the active ingredients should be provided in two separate portions. There is certainly no disclosure in Keller of a method for producing a dry powder inhalation composition wherein a first particulate inhalant medicament is provided in a first portion in an amount sufficient to create a monolayer on the particulate carrier. If anything, Keller's teachings would have suggested to a person

skilled in the art that the order of mixing is not critical, and does not influence the properties of the final product.

The Examiner maintains that although Trofast lacks an explicit teaching of the order of steps used in preparing the dry powders, this deficiency is cured by the teaching of Keller because Keller's teaching of mixing different ingredients in any desired sequence "encompasses" the claimed step sequences. However, Applicant is unaware of any legal authority or precedent that supports or otherwise endorses the proposition that prior art teachings that encompass a claimed invention necessarily render it obvious. To the contrary, there is ample precedent that such inventions might well be nonobvious and thus patentable over broad or generic prior art teachings. Thus, Keller does not cure the deficiency of Trofast.

The Examiner then relies upon Ward to deal with the issue of the claimed particle size of the carrier. However, reliance upon Ward is misplaced in at least two respects. First, Trofast and Keller are both concerned with the provision of dry powder formulations comprising lactose as a carrier substance (see the examples of both documents). In contrast, Ward is directed to dry powder formulations that do not include lactose. Indeed, a key feature of the formulations disclosed in Ward is the avoidance of the disadvantages associated with the use of lactose (see the abstract, line 65 of column 2 to line 12 of column 3, and lines 31 to 33 of column 3 of Ward). Instead of using "inert" carrier particles, Ward's pharmaceutical formulations contain micro fine particles and carrier particles wherein both types of particles are made of an active pharmaceutical compound. Upon inhalation, the active micro fine particles and carrier particles are separated, whereupon the micro fine particles travel through the throat and into the lungs and the carrier particles pass into the throat and are

swallowed for delivery to the GI tract. Ward is not concerned with compositions comprising a first particulate inhalant medicament, a second particulate inhalant medicament, and an inert carrier, as recited in the presently claimed invention.

Second, Ward's teaching of the use of relatively larger carrier particles is directly contrary to the teaching in Trofast to the effect that all ingredients in its formulation, including the carrier such as lactose, are rendered less than 10 μm in size. *See, e.g.*, Trofast, column 2, lines 3-10, "[t]he ingredients of the formulation according to the invention *must* both be in a finely divided form, *i.e.* their mass median diameter should generally be less than 10 μm, preferably from 1 to 7 μm . . ." (emphasis added). Plainly, *Trofast* emphasizes the importance of having all of the ingredients with the same particle size.

The routineer in the art, seeking to modify Trofast's formulations, would not have diverged from its teachings and proceeded in a totally opposite direction regarding the nature and size of the carrier particles. Thus, the attempt to establish *prima facie* obviousness based on the combination of Trofast and Ward could only be arrived at via hindsight reconstruction. To reach the Examiner's conclusion, a person of ordinary skill would need to proceed directly contrary to the teachings in Trofast by replacing the carrier particles with particles made of an active agent that are much larger in size. However, doing so would clearly be inconsistent with the objectives of both patentees. Prior art publications must be evaluated in their entirety. Thus, it is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation

of what such reference fairly suggests to one skilled in the art. *See, In re Mercer* 515, F.2d 1161, 1165-66, 185 U.S.P.Q. 774, 778 (C.C.P.A. 1975).

In view of the foregoing, the person of ordinary skill in the art would not have been motivated to modify Trofast's formulations in accordance with the teachings in Ward.

In view of all of the foregoing, Applicant respectfully submits that claims 1-32 would not have been obvious over Trofast in view of Ward and Keller. Withdrawal of this rejection is therefore respectfully requested.

As it is believed that all of the rejections set forth in the Office Action have been fully met, favorable reconsideration and allowance are earnestly solicited.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that he/she telephone Applicants' attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

If there are any additional charges in connection with this requested amendment, the Patent Office is authorized to charge Deposit Account No. 12-1095 therefor.

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Respectfully submitted,

By_____

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